American Journal of Medical Genetics 62:300–301 (1996)

Letter to the Editor

De Novo Direct Duplication of Chromosome Segment 22q11.2–q13.1

To the Editor:

Lindsay et al. [1995] reported a case of de novo duplication of the segment 22q11–q12. Molecular cytogenetics studies showed that the segment includes the regions responsible for the "cat eye," DiGeorge, and velo-cardio-facial syndrome, and extends distal to the breakpoint cluster region. The phenotype was milder than that of complete trisomy 22 and der(22)t(11;22)(q23;q11) syndrome and was similar in type and severity to that of "cat eye" syndrome (CES). They suggested that trisomy of gene(s) responsible for the CES might have a predominant phenotypic effect over other genes present in the region duplicated in their patient.

We have a similar patient with de novo duplication of 22q who shows minor physical anomalies. The patient was born at term to a 26-year-old gravida 2 para 1 mother and 31-year-old father. The mother had amniocentesis at 37 weeks of gestation because of fetal hydronephrosis. Chromosome analysis done in another laboratory showed an abnormal karyotype of 46,XY, dup(22)(q11.2q13). Parents' chromosomes were normal. At birth, the infant weighed 3,686 gm and measured 52 cm in length. During the first 2 months of life he was evaluated in two outside medical facilities five times including two hospitalizations for "apnea" and failure to thrive. At 2½ months he was referred to our Medical Center. He weighed 3.9 kg, measured 59 cm in length, and had an OFC of 36.5 cm. He had bilateral preauricular pits and a highly arched palate but otherwise his facial appearance was not dysmorphic. Bilateral hydronephrosis and grade IV vesicoureteral reflux were diagnosed. The patient was treated for urinary tract infection and vesicotomy was placed. No cardiac lesion was diagnosed. He had recurrent urinary tract infection and placed on antibiotic prophylaxis. He started to gain weight and at 7 months, he weighed 5.7 kg and had length of 63½ cm and an OFC of 40 cm. He was able to roll over but was unable to maintain a sitting position due to poor trunk control. At 14 months, his weight, height, and OFC were 7.2 kg, 71 cm, and 42.5 cm, respectively (all below the 5th centiles). His development was determined to be at 6 to 7 months level by the Denver II Developmental Schedule.

Chromosome studies were performed from peripheral blood using standard cytogenetic procedures and ethidium bromide to obtain prometaphase preparation. By G-banding, the presence of extra material on 22q (22q+) was noted in all cells examined. High resolution banded chromosomes based on band sizes and differential staining intensity suggested a duplication of 22q11.2→q13.1 (Fig. 1). Fluorescence in situ hybridization (FISH) using chromosome 22-specific painting probe (Oncor) showed that it labeled both the normal and 22q+ chromosomes uniformly along the full length of 22q (Fig. 2A). This confirmed the cytogenetic findings that the additional chromosomal subregion originated from chromosome 22q11.2→q13.1 as duplication. To determine whether DiGeorge chromosome region was involved in duplication, FISH using D22S75 (22q11.2) DiGeorge chromosome probe (Oncor) and D22S39 (22q13.3) chromosome 22 control probe (Oncor) was performed. Figure 2B shows 2 DiGeorge signals (arrows: 1st signal proximal to the centromere, the 2nd signal next to the 1st and distal to the centromere), and one control signal (22qter) on the dup(22). The normal 22 has one DiGeorge signal proximal to the centromere and one control signal on 22qter. The relative distance of probe signals between DiGeorge and the control on

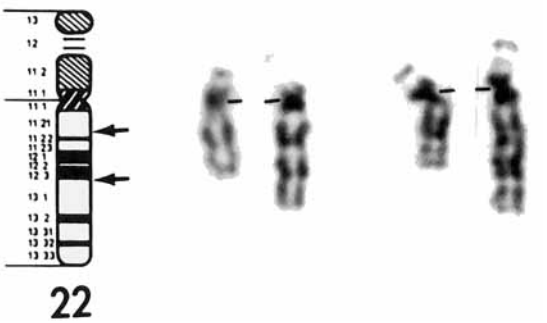

Fig. 1. G-banded idiogram and partial karyotype of chromosome 22 showing extra positive bands in the proximal long arm of one of the 22 chromosomes (on the right of each pair). Arrows in the idiogram indicate the duplicated region.

Received for publication May 30, 1995; revision received October 9, 1995.

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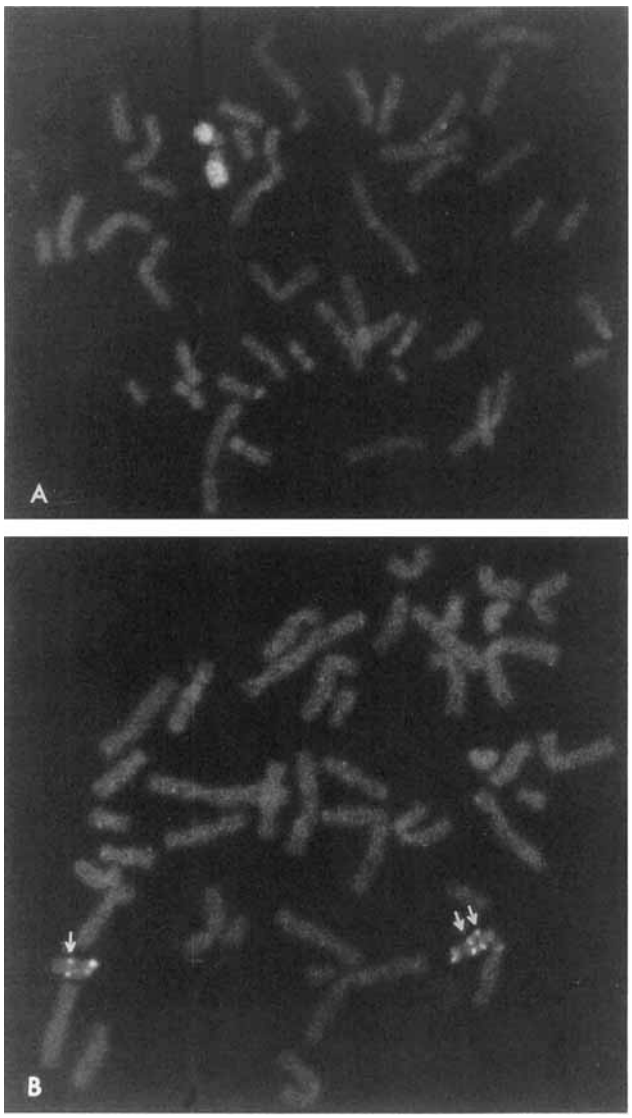

Fig. 2. **A:** Chromosome 22-specific painting probe showing normal 22 and dup(22). **B:** D22S75 (DiGeorge chromosome region) and D22S39 (control, 22q13.3) probes showing 2 DiGeorge (arrows) and one control signal on dup(22) and the normal 22 with one signal from each probe.

the normal 22 chromosome is equal to that of 2nd DiGeorge signal to the control signal on the dup(22) chromosome in the same metaphase (Fig. 2B), indicating that the dup(22) is a direct duplication. If it is inverted duplication, the relative distance of the 2nd DiGeorge signal to the control signal on the dup(22) should be shorter than that on the normal 22 chromosome. Since D22S75 in DiGeorge chromosome region is associated with del(22)(q11.21q11.23) [Driscoll et al., 1992], the karyotype interpretation of the patient is 46,XY,dup(22)(q11.21q13.1).

Complete trisomy 22 syndrome, der(22) syndrome, and CES show some overlap in manifestation. In general the severity of the phenotype correlates with the size of the duplication. For this reason, the milder phenotype seen in our patient was not predicted prenatally. The mother was counseled after the amniocentesis by another clinical geneticist that her fetus had a lethal condition known as trisomy 22 syndrome. When he was hospitalized at 2½ months, the mother did not relate closely to the infant and asked when he was going to die. The frequent visits to emergency rooms for complaint of "apnea" appeared to result from the mother's high level of anxiety.

Profound mental retardation seen in der(22) syndrome may be partly due to presence of extra 11q material. Severe phenotype of complete trisomy 22 syndrome may result from duplication of regions distal to q13.1. Both the patient reported by Lindsay et al. [1995] and our patient had only minimal facial anomalies but our patient seems to have a milder phenotype since he does not have a cardiac defect which is seen in the "cat-eye" syndrome. The duplication in our patient involves DiGeorge region but may not involve cat-eye syndrome region which is located closer to the centromere than the DiGeorge region [Scrambler, 1994].

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